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EXHIBIT M

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Quantitative Structure - Activity Relationship (QSAR) Studies on Non Steroidal Anti-Inflammatory Drugs (NSAIDs)

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Abstract: Different chemical structures have been found to possess different anti-inflammatory activities. Inflammation is a normal and essential response to any noxious stimulus which threatens the host and may vary from a localized response to a more generalized one. In view of the complexity and multitude of biochemical factors involved in inflammatory events, few general correlations of chemical structures and physicochemical properties with biological activities would be expected. Nevertheless some general features seem to be commonly associated with a large number of active drugs. However, these main features are not sufficient, but they could reflect certain physicochemical requirements for in vivo efficacy.

QSAR is a useful means for maximizing the potency of a new lead compound. In the lead optimization phase of the synthetic project various QSAR procedures with the aid of computer-technology have been proposed. Among them, the classical Hansch approach has been widely used leading to quite a few successful examples. In the QSAR approaches, the prescription to optimise the lead structure is inferred from mathematical equations correlating variations in the potency of a certain biological activity with physicochemical and structural descriptors among congeneric molecules. The QSAR procedures are based on physical organic concepts and involve calculational operations. In the last years, quantum-chemical descriptors have been used in QSAR studies, because of the large physical information content encoded in many of the descriptors.

Several anti-inflammatory receptor site models have been proposed. Since inflammation is a complex phenomenon involving interrelationships between humoral and cellular reactions through a number of inflammatory mediators, there is not much evidence on QSAR studies. Several QSAR studies have been reported obtaining only partial results. It was found that substituents which contribute to the high lipophilicity, were favourable to the activity. Substituents of short length (H, CH_3) have also a favourable effect. Satisfactory relationships between the in vivo activities and deprotonation energies, the HOMO energies and lipophilicities were found.

Introduction

Inflammation- Non-steroidal Anti-inflammatory Agents (NSAIDs)

The description of the phenomenon in terms of underlying cellular events in the injured tissues, is very difficult. Although, there are certain features of the process that are generally characteristic. These include fenestration of the microvasculature, leakage of the elements of blood into the interstitial spaces and migration of leukocytes into the inflammed tissue, accompanied by erythemas, edema, hyperalgesia and pain. During this complex response, chemical mediators (histamine, 5-hydroxytryptamine, slow-reacting substance of anaphylaxis), chemotactic factors, bradykinin and prostaglandins (PGs) are liberated locally. Many mediators of the inflammatory process have been identified.

Inflammation in patients with rheumatoid arthritis probable involves the combination of an antigen with an antibody and complement, causing the local release of chemotactic factors that attract leukocytes. The leukocytes phagocytatize the complexes and also

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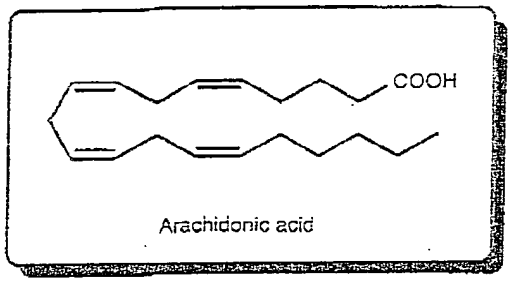
release many enzymes contained in their lysosomes. These enzymes cause injury to cartilage and other tissues. Cell-mediated immune reactions may also be involved. PGs are also released. They are mediators of inflammation and are produced following the initial transformation of arachidonic acid by cyclooxygenase (COX) to prostaglandin H_2 [1]. For many years it was believed that COX was a single enzyme. Recently it was found that COX exists in two isoforms [2]: isozyme COX-1 is responsible for physiological regulation (e.g. protects the gastrointestinal tract), whereas the inducible COX-2 isoform mediates inflammatory PGs production by inflammatory mediators under pathophysiological conditions. The lipoxygenase (LOX) pathway results in formation of hydroxyperoxyeicosatetraenoic (HPETES) and hydroxyeicosatetraenoic (HETES) acids and particularly leukotrienes. Leukotriene B_4 is a potent chemotactic substance. COX and LOX are key enzymes in the arachidonic acid cascade, which results in the formation of inflammatory PGs and leukotrienes.



Arachidonic acid

Reactive oxygen species (ROS) have been involved in the development of inflammatory disorders [3]. Oxidative stress is considered one of the pathogenic factors of inflammation. A recent investigation has shown that superoxide desmutase (SOD) which scavenges superoxide anions and suppresses the deleterious effects that might be produced by further reaction of O_2^- or other ROS with cellular components, acts to alleviate edema formation in rat carrageenin-induced hind paw edema [4] and adjuvant arthritis models [5]. Free radical intermediates are formed during the transformation of arachidonic acid into PGG_2 and PGH_2. As a consequence it might be possible to diminish tissue damages on treatment with effective radical scavengers.

Inflammatory responses occur in three distinct phases 1) an acute transient phase, characterized by local vasodilatation-increased capillary permeability, 2) a delayed subacute phase characterized by infiltration of leukocytes and phagocytic cells and 3) a chronic proliferative phase, in which tissue degeneration and fibrosis occur.

Because the clinically useful NSAIDs differ widely in chemical and physical properties, attempts have been made to compare the biochemical properties of these compounds in order to determine possible modes of action. The non-steroidal anti-inflammatory drugs (NSAIDs) are a heterogeneous group of compounds, often chemically unrelated. The prototype is aspirin. Hence these compounds are often referred to as aspirin-like drugs. Their mechanisms of action differ from these of the anti-inflammatory steroids. NSAIDs modify the inflammatory responses to disease but are not curative and do not remove the underlying cause of the disease. An ideal anti-inflammatory drug should affect only aberrant, uncontrolled inflammation and not interfere body's vital defence mechanism to invading micro organisms and other environmental insults.

These drugs are polyvalent. They are able to modulate more than one molecular or cellular event thought to be concerned in the inflammatory event. NSAIDs have a number of biochemical activities. They inhibit formation of the inflammatory mediators and moderate the activity of the inflammatory proteases. They also stabilize lysosomal membranes and inhibit the biosynthesis of prostaglandins. In the early 70's, it was reported that NSAIDs prevent the production of PGs by inhibiting the enzyme COX. The fact that anti-COX agents do serve as useful anti-inflammatory agents indicates that COX action is often one of the important rate-limiting reactions mediating the eventual expression of the symptoms of inflammation. The inhibitors of COX can be classified in three categories : depending on whether they produce a rapid reversible competitive inhibition, a time-dependent inactivation or a rapid reversible non-competitive inhibition (antioxidants). The competitive inhibitors represent an easily understood interaction at the substrate site in which a related polyunsaturated fatty acid can bind at the site but cannot form a product. Competitive inhibition at the substrate site can also occur with substituted carboxylic acids e.g. arylpropionate derivatives. Binding of this type of inhibitor to the COX appears to depend more on hydrophobic features than on its ionic character since binding of these agents was not appreciably influenced by converting the carboxylate moiety to the methyl ester. However, the NSAIDs do not generally inhibit the formation of eicosanoids such as the leukotrienes, which also contribute to inflammation. PGs have been proved to be protective and antisecretory; thus inhibition of COX disturbs this cytoprotective mechanism. Another hypothesis focuses on the shunt to the leukotrienes, metabolites of arachidonic acid (LOX pathway). Recently effort has been made to develope compounds with both COX and 5-LOX inhibiting activities in order to have improved efficacy and reduced side effects when compared to selective COX inhibitors. The di-tert-butyl-phenol derivatives [6] have been reported to be dual inhibitors of both COX and 5-

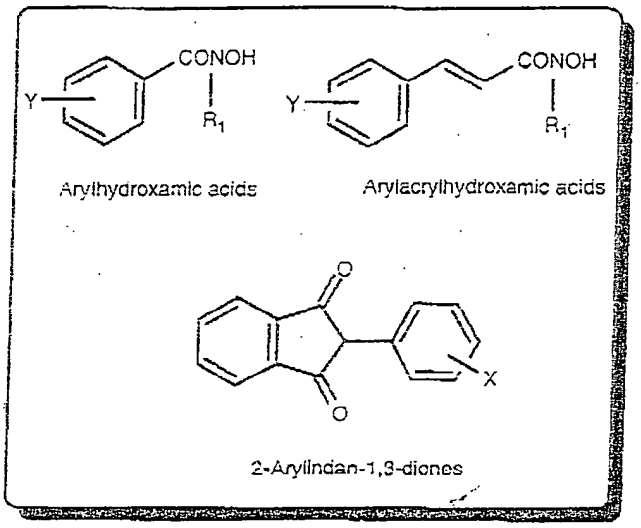
LOX . Another approach is to incorporate into the pharmacophore of various NSAIDs, 5-LOX inhibiting activity by converting them to the corresponding hydroxamates

NSAIDs may displace anti-inflammatory peptides from albumins, or hyperpolarize neuronal membranes in the acidic environment of inflammed tissue. They are also believed to inhibit oxidative phosphorylation. Furthermore, these drugs may have other actions that contribute to their therapeutic effects. Aspirin-like drugs induce gastric or intestinal ulceration by at least two distinct mechanisms : a) local irritation by orally administrated drugs and b) by inhibition of the biosynthesis of gastric prostaglandins (PGI_2 & PGE_2).

Classification of NSAIDs

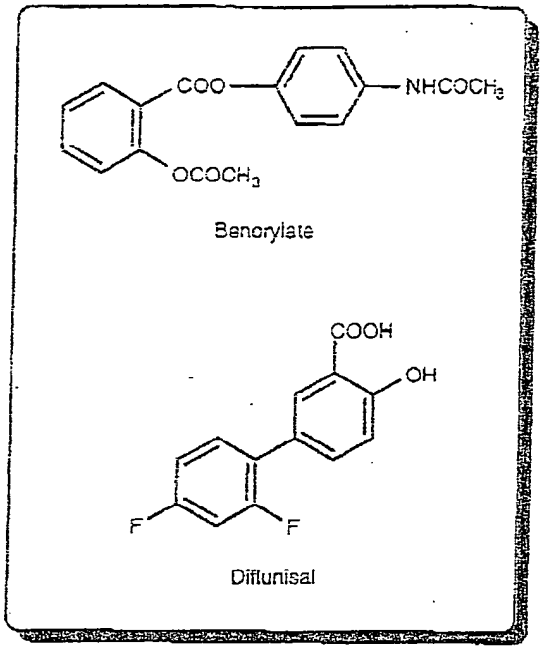
Aryl Acidic Drugs

Analogous to tricyclic amines in mental health and aralkylamines as antihistamines, a large group of aryl and aralkyl acids have been found to be non-steroidal anti-inflammatory-analgesic acids.



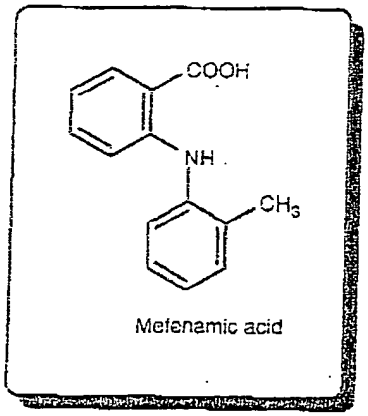
Salicylic Acid Derivatives

The irreversible attempts have been, inactivation of COX by aspirin through transacetylation of the lysyl-amino group in the enzyme. Substitution on the carboxyl or hydroxyl groups change the potency or toxicity of the compound. The o-OH group is very important for the action of salicylate. Numerous attempts have been made to seek a superior aspirin. The objectives are threefold : high potency, better tolerance, longer duration of action. The simplicity of aspirin molecule has defied extensive synthetic efforts to discern any quantitative structure-activity relationships toward the design of a superior analogue. The effects of simple substitutions on the benzene ring have been extensively studied. The result of these multiple approaches are exemplified by a complex salt, trisilate, an ester (benorylate) and diflunisal.



Fenamates

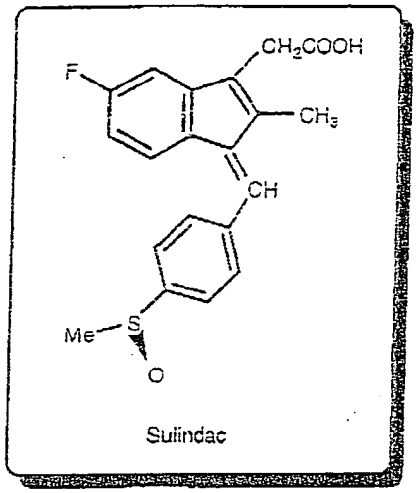
Fenamates are a family of N-anthranilic acids : mefenamic acid, flufenamic acid and meclofenamic acid. Heterocyclic isosters of fenamates are exemplified by niflumic acid, clonixin and flumixin. An aza-analogue is the analgesic glaphenine, a combination of 8-chlorooquinoline and anthranilic acid; floctafenine (CF_3 analogue) and hydroxy alkyl esters. The m-CF_3 group in the aniline moiety was found to be optimal for activity in fenamates. Fenamates bind strongly to albumin and other protein sites and are potent COX's inhibitors.



Indomethacin, Sulindac and Analogues.

The original 1-benzylindole-3-acetic acid lead was discovered in an attempt to use structures related to serotonin metabolites for anti-inflammatory activity.

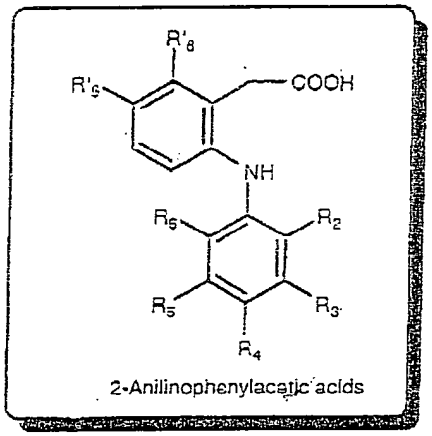
Indomethacin was found to be a potent inhibitor of the biosynthesis of PGs, whereas sulindac is a reversible pro-drug.



Sulindac

Phenyl-propionic Acids

Substituted phenyl-propionic acids constitute the largest family of aryl acidic anti-inflammatory agents. most of them are also fatty acids COX inhibitors. A few have been shown to be reversible inhibitors competitive with the substrate arachidonic acid.

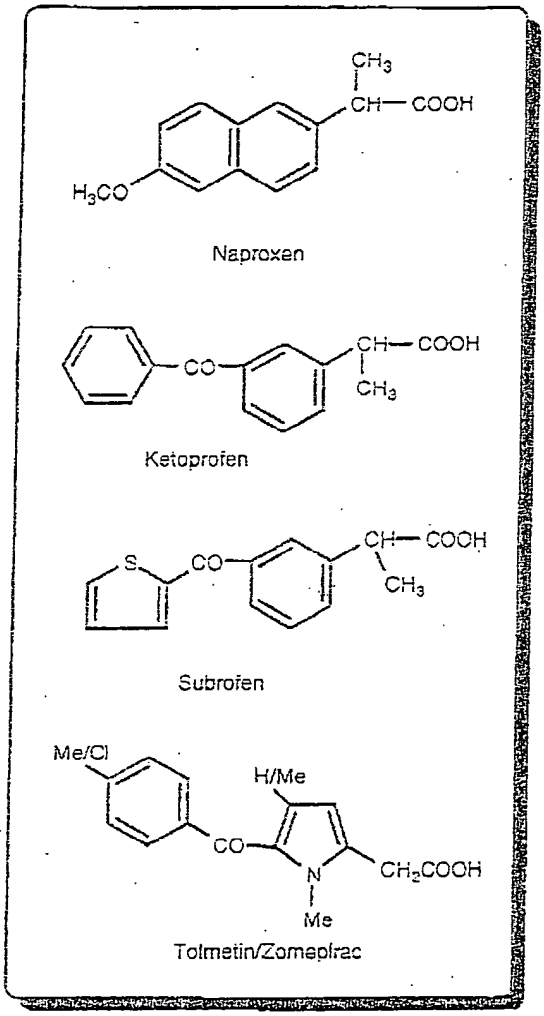


2-Anilinophenylacetic acids

Three basic chemical features of phenyl- propionics may be discussed in terms of structure-activity relationship : the propionic acid side chain, phenyl substituents (X) and a second hydrophobic group (Ar).

Ar-[(X)- C_6H_3-]- $C(CH_3)$- COOH

In most series, the corresponding acetic acid analogue is less potent. Most effective phenyl ring substituents are limited to an electronegative F or Cl, meta to the acid side chain, which may also exert a steric effect to favour a non-planar arrangement of the second hydrophobic group. A variety of second hydrophobic substituents at C4- have been found effective. Linear aliphatic or aromatic substituents, cyclohexyl and heteroaryl groups, introduced and found to be potent. A suitable example is the well known naphthalene derivative, naproxen. A notable variation of the linear diaryl arrangement is to attach the second hydrophobic group an angular carbonyl or ether linkage at C3 such as ketoprofen, suprofen and the heteroaryl analogues : tolmetin and zomepirac. Cyclization of ketoprofen with a seven-membered ring to maintain a non-planar configuration gives tricyclic compounds. The dibenzoxepins appear to be slightly more potent than the dibenzothiepins. 3-Substituted dibenzoxepins and dibenzothiepins, with the acid side chain to a p- position to the carbonyl- bridge, are twice as active as 2-substituted analogues.

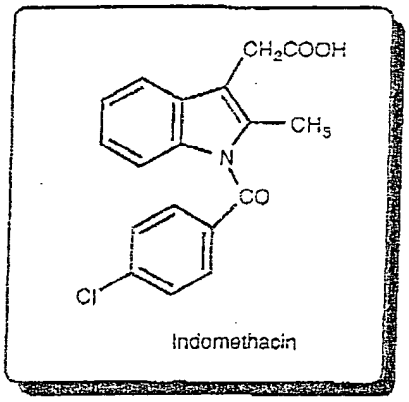


Translocation of the oxygen or sulfur atom and the methylene group of the central ring caused a dramatic ten to fourty fold decrease in potency. The broad scope of active diaryl arrangements is indicated by the potent C2- substituted phenyl- acetic acid, diclofenac, a hybrid of fenamate and phenyl-acetic acid.

In the study of aryl-acidic NSAIDs, replacement of the carboxyl (pK_a 3-5) by a sulphonamide group (pK_a 8-

10), invariably loses activity. Stimulated by the highly electronegative (Hammet σ = 1.3) and lipophilic (π = 0.95) characters of the CF_3SO_2 group, a series of fluoroalkane sulfonyl anilides were investigated, although no correlation was descernible with their biologic activities.

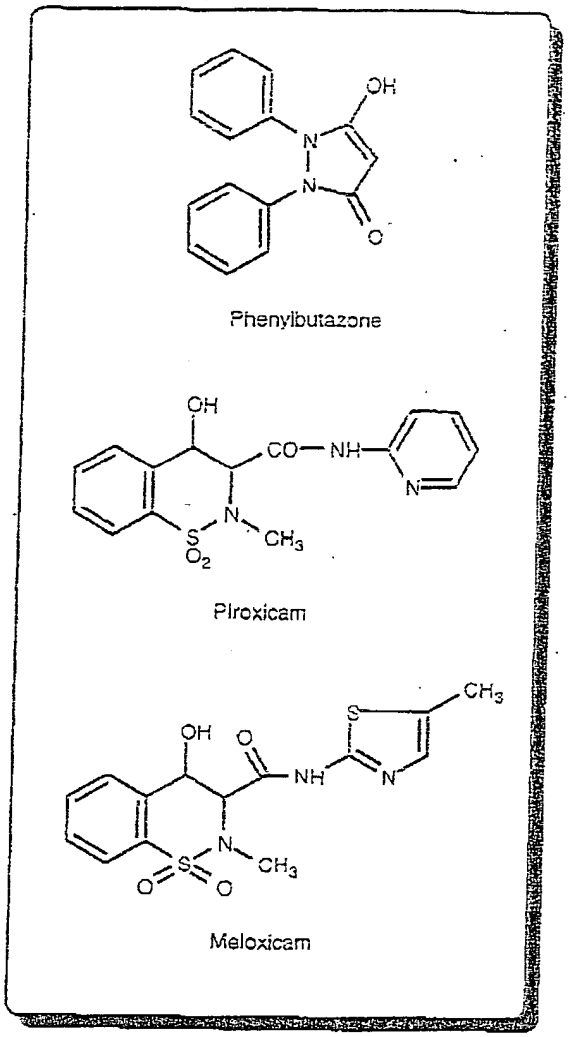
A consistent correlation of two stereochemical aspects with optimal biological activity was noted with the above mentioned groups of compounds. First when a chiral centre is created by changing the side chain acetic acid to α-propionic acid, bioactivity is generally associated with the S (+) enantiomer. This stereospecificity is valid for many aryl-α-propionic acids. Second, as shown by X-ray crystallography of indomethacin and isosteres, the two phenyl moieties are non-coplanar and in the cis- form. This preferred configuration has been refined with CNDO calculation and computer modeling to give a hypothetical receptor contour for indomethacin, which also accommodates arachidonic acid, the substrate of COX.



Indomethacin

Enolic and Other Acidic Agents

These agents posses ionizable protons from an enolic or potentially enolic β-diketones. Their acidity (pK_a 4-7) is comparable to various carboxylic groups. The presence of two aryl-moieties provides the lipophilic characteristics for protein binding and tissue distribution. Two well known groups are I) pyrazolidinediones (e.g. phenylbutazone) II) hydroxybenzothiazines (e.g. piroxicam) and the structurally related compound meloxicam. The pharmacological profiles of these compounds are generally similar to those NSAIDs, possessing a carboxylic acid function. Thus, they inhibit PGs synthesis. The acidity of phenylbutazone, pK_a 4.5 and the non-planar arrangement of the two phenyl rings signified important features in the search for potent molecules. The 1,2-benzothiazine analogues were found to be highly potent compounds. The acidic enolate anion is stabilzed by internal hydrogen bonding with the amide proton. Their pK_a values are in the range of 5 to 6.



It has been demonstrated that meloxicam is a potent inhibitor of COX-2 and is, in comparison to all NSAIDs, available on the market, the first one to inhibit COX-2 more effectively than COX-1 [7] whereas piroxicam is a selective inhibitor of COX-1.

Non-acidic Anti-inflammatory Agents

Compared with aryl-acids, the pharmacological profile of the non-acidic compounds is more structure dependent and they generally produce less gastrointestinal irritation. Even with the absence of the carboxyl group, some are potent PGs inhibitors. The non-acidic agents may be categorized as substituted triaryls, quinazolinones and a miscellaneous group with different biochemical properties. Several combinations of three aryl groups, such as two phenyl and a five membered heterocycle, in a fused or angular stereochemical configuration (e.g. substituted indolyl-derivatives and substituted phenyl-oxazolopyridines) have been found to exert anti-inflammatory activity. Among various analogues proquazone and ciproquazone were found to be effective and to act as reversible inhibitor of prostaglandin synthetase.

Diflalone was also found to be a non-acidic moderately active anti-inflammatory compound. Etodolac and nabumetone are new compounds, inhibitors of COX, possessing anti-inflammatory activity.

QSAR - Results and Discussion

36 compounds analogues of diclofenac were chosen according to the following criteria : the structural variations should be suitable to systematically explore the spatial and physicochemical requirements for the COX binding site for NSAIDs and were subjected to a QSAR analysis. The following equation [8] explained the PGs data most satisfactorily:

$\log 1/IC_{50}PGs = -8.43 + 1.99 \log P - 0.79 \log P^2 + 0.094\ a + 1.02\ I\text{-}hal_5' - 1.66\ I\text{-}OH_A - 0.611\ I\text{-}OH_B$

$n = 36, s = 0.525, r = 0.848, \log Popt. = 1.26$

log P = calculated lipophilicity, $I\text{-}OH_A$ = OH in position 5' or 6' of ring A; $I\text{-}OH_B$ = OH in position 3 or 4 of ring B; I-hal5' = halogen in position 5' of ring A ; a = possibility to express the twisting of the phenyl ring.

A plot of the adjuvant arthritis ED_{40}(AdA) vs the IC_{50} PGs activity tests reveals a reasonable correlation :

$\log [\ 1/ED_{40}\ (AdA)\ ] = -0.36 + 0.69 \log 1/IC_{50}$ PGs

$n = 34, r = 0.687, s = 0.75$

suggesting that the inhibition of the COX is indeed the underlying mechanism in this arthritis model, at least for more potent compounds. With the same set as for the PGs data and the same variables, the following «best» QSAR equation was obtained for $\log 1/ED_{40}$AdA :

$\log [1/ED_{40}(AdA)] = -9.05 + 2.20 \log P - 0.80 \log P^2 + 0.1a - 0.8\ I\text{-}OH_B - 2.65\ I\text{-}su6' + 0.93\ I\text{-}hal5'$

$n = 34, s = 0.492, r = 0.873, \log Popt. = 1.38$

I-su6', is an indicator for the presence of a substituent in position 6' of ring A.

The lipophilicity optimum is almost the same for the PGs data in the range initially identified for good anti-inflammatory activity. Ring twisting by large o-substituents in ring B is also a promoting factor as well as halogen substitution in position 5'. Both activities can largely been explained by the same simple physicochemical and geometrical parameters : lipophilicity and twisting of the two aromatic rings due to a substitution of ring B.

Simple stable molecules containing the hydroxamic acid functionality have been shown to inhibit 5-LOX. The results of a quantitative evaluation of structure activity relationship study [9] involving more than 100 hydroxamic acids of diverse structure are given below.

Aryl Hydroxamic Acids

$\log 1/IC_{50} = 0.41\ \pi - 0.92$ I-NH + 4.51

$n = 38, r = 0.815, s = 0.500, F_{2,35} = 37.5$

π refers to the hydrophobicity constant of the entire aryl fragment; I-NH variable having a value of 1 when R_1 = H (R_1 the substituent on the hydroxamate nitrogen)

If the values of π are adjusted so that only the lipophilicity of the first three carbons of the alkoxy chain are included (π') a much improved correlation is achieved :

$\log 1/IC_{50} = 0.66\ \pi' - 0.83$ I-NH + 3.68

$n = 38, r = 0.942, s = 0.301, F_{2,35} = 137.0$

Aryl Acrylohydroxamic Acids

In this group an unsaturated spacer unit connects the hydroxamate moiety with the aromatic ring. Equation describes the QSAR for the entire set :

$\log 1/IC_{50} = 0.36\pi' - 1.46$ I-NH - 0.98 I-BIG2 + 5.36

$n = 29, r = 0.944, s = 0.299, F_{2,26} = 67.8$

I-BIG2 indicates the presence of a large R_2 substituent; π' adjusted π values (by omitting the contribution of the hydrophobicity of all but the first carbon of the R_2 substituent).

Aryl Alkyl-hydroxamic Acids

The above compounds have a saturated alkyl spacer unit between the aromatic ring system and the hydroxamate functionality.

$\log 1/IC_{50} = 0.61\pi'' - 1.26$ -INH - 0.62 I-BIG2 + 3.43

$n = 35, r = 0.95, s = 0.266$

π'' adjustment so that only one of the two methyls of the isobutyl was included.

IV) Aryloxy-alkyl hydroxamic acids

An ether linkage is used to connect an aromatic ring system to a hydroxamate-bearing alkyl chain.

$\log 1/IC_{50} = 0.57\pi - 0.60$ I-NH + 3.71

$n = 8, r = 0.853, s = 0.319, F_{2,5} = 6.69$

Since there is similarity in the QSAR of all the compounds, a cumulative QSAR of groups I-IV was derived.

$\log 1/IC_{50} = 0.55\ \pi - 1.05$ I-NH - 0.64 I-1 + 4.25

$n = 111, r = 0.916, s = 0.379, F_{3,107} = 185.9$

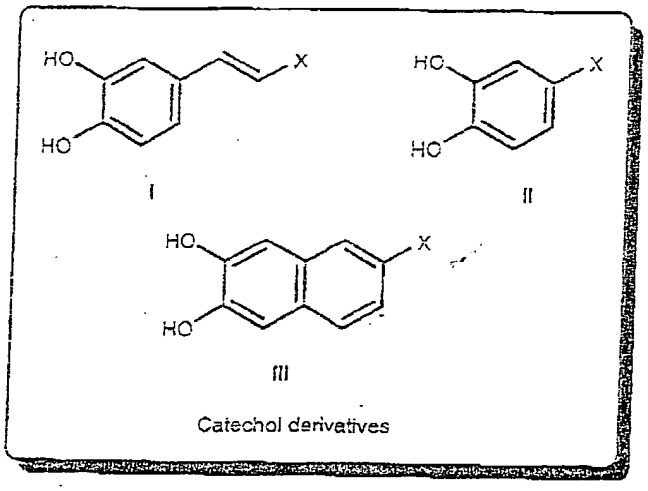
I-1 is a variable that indicates if the hydroxamate is directly attached to the aryl ring or attached through an unsaturated spacer unit. The most important physical property determining inhibitory potency, is the lipophilicity of the molecule. The QSAR suggests that hydroxamic acids may interact with a large hydrophobic surface or trough on the enzyme. However, two major areas were identified where hydrophobicity does not appear to improve inhibitory activity. Large hydrophilic substituents extremely close to the hydroxamate moiety may be encountering hydrophilic areas of the enzyme.

For various catechol derivatives, from the I50 values of production of leukotriene B_4 and 5-hydroxyeicosatetraenoic acid from arachidonic acid by guinea pig polymorphonuclear leukocytes, the following equation [10] is derived :

$$\log 1/C = 0.491 \log P - 0.75 \log (\beta.10^{\log P} + 1) - 0.62\ D\text{-}II - 1.13\ D\text{-}III + 5.50$$

$n = 51$, $r^2 = 0.801$, $s = 0.269$, $\log Popt. = 4.61$

D-I = 1 for compounds in which a styrene group is present; D-II = 1 for compounds without a styrene double bond; D-III = 1 for compounds with a naphthalene skeleton. Because their coefficients are negative (D-II & D-III), series I, has the greatest intrinsic potency. Compounds included in this study are non-competitive inhibitors of 5-LOX and they were suggested to interact with a hydrophobic milieu of the 5-LOX.



Catechol derivatives

The importance of hydrophobicity of inhibitors of LOX is apparent from another study [11]of I_{50} of ROH inhibition of soybean LOX.

$$\log 1/k_i = 0.83 \log P + 0.39$$

$n = 12$, $r^2 = 0.990$, $s = 0.087$

Seventy two, 1-phenyltetrahydropyridazin-3(2H)-one analogues [12] are examined for inhibitory potency IC_{50} of 5-LOX, in a broken cell. The potency is increased by lipophilic substituents at the 3'- and 4'-positions. Substituents with positive F values at the 4'-position also increase the potency. On the contrary a substituent with a positive R value at the 3'- position decreases it. A decrease is also observed as the size of the 2'-and/or 4'- substituents increases. There is an optimum size of the cavity for the 4'-substituents, the size of CO-hexyl or CO-heptyl being the optimum. Thioketone derivatives show about five times higher inhibitory activity than the corresponding carbonyl analogues.

$$\log 1/IC_{50} = -1.17\ B_{2\text{-}2'} + 0.40\ \pi_{3'} - 0.61\ R_{3'} + 0.51\ \pi_{4'} - 4.70\ B_{2\text{-}4'}^2 + 0.75\ F_{4'} + 0.66\ MR_{4'} - 0.10\ MR_{4'}^2 + 0.73\ I\text{-thioketone} + 0.58\ \pi_{5} + 9.86$$

$n = 72$, $s = 0.321$, $r = 0.921$, $scv = 0.384$, $F = 30.46$

$B_{2\text{-}4'}opt.. = 2.25$; $MR_{4'}$ opt. $= 3.38$

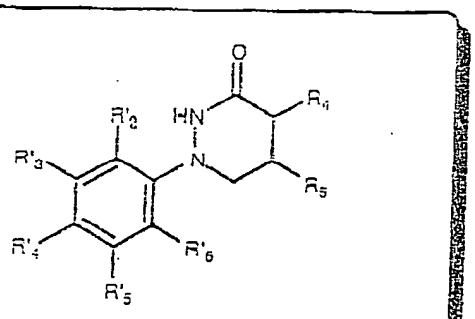
QSAR of sixty 1-phenyl -[2H]-tetrahydrotriazin-3-one analogues [13] are also examined for their inhibitory potency IC_{50} on 5-LOX, in a broken cell.

$$\log 1/IC_{50} = 0.56\ \pi_{5'} + 0.44\ \pi_{5} + 0.84\ \pi_{3'} + 1.01\ MR_4 - 0.24\ MR_4^2 - 0.49\ MR_2 - 0.39\ I\text{-}4OR + 0.47\Sigma\sigma_m - 0.71\Sigma\sigma_p + 0.20\ I\text{-thiourea} + 4.47$$

$n = 60$, $RMSE = 0.245$, $r = 0.863$

$RMSEcv + 0.286$, MR_4 opt. $= 2.10$, $F = 14.3$

The parameters $\pi_{3'}$, $\pi_{5'}$, π_{5} are for the lipophilic effects of 3'-, 5-' and 5- substituents, respectively $\Sigma\sigma_m$ is the sum of Hammett σ_m values [14] for the 3'- and 5-' phenyl or α-pyridyl substituents, $\Sigma\sigma_p$ is the sum of Hammett σ_p values for the 3-' and α-pyridyl substituents, and MR_2 and MR_4 are the molar refractivity (MR) [14] of 2- and 4-substituents respectively. I-4OR and I-thiourea are indicator variables for 4-OR substituents and for thiourea analogues, respectively. As we can see from the equation,



Phenyltetrahydropyridazin-3(2*H*)one analogues

potency is increased by lipophilic substituents at the 3'-, 5'- and 5- positions, and with 3'- and 5'- substituents that withdraw electrons. On the contrary it is decreased with 3'- substituents on the pyridyl ring, that donate electrons. The size of 2'- substituents affects the potency. It decreases as the size increases. Thiourea analogues compared to the corresponding carbonyl analogues, are more potent.

QSAR studies have been reported for different series of 5-LOX inhibitors and from these it is evident that there is a strong positive correlation between lipophilicity and activity. The biological results used in the study are derived from cell-free assays, so they cannot be explained by the enrichment in the cell membrane alone, but also by lipophilic interactions at the binding position of the enzyme. This is in accordance with the finding that one of the key structural features of the active site of the 5-LOX is a hydrophobic domain (beneath of non-heme ferric ion and a carboxylic acid binding site).

In an attempt to correlate the anti-inflammatory activity (as induced percent inhibition of carrageenin mouse paw edema), of some 2-(aminoacetylamino)-thiazole [15] derivatives with their lipophilicity as R_M, the following equation was derived :

$\log \% = -1.518\ R_M + 0.793$

$n = 7,\ r = 0.958,\ s = 0.048,\ F = 33.43$

R_M values were determined from the corresponding R_F values from reversed phase thin layer chromatography.

The following equation was performed in order to find out if any correlation exists between anti-inflammatory activity, as carrageenin induced mouse paw edema CPE, of some 2,4-disubstituted thiazolyl aminoketones [16] and their anti-proteolytic activity Apr. The role of proteases in inflammation is well documented.

$CPE = 0.62 + 0.58\ Apr$

$n = 7,\ r = 0.964,\ s = 0.03,\ F = 64.84$

2,3- Dihydro-benzofuranones, analogues of the natural product wortmannin were found to inhibit prostaglandin synthesis in vitro. A structure activity study was carried out [17] and expressed as a parabolic function of log P and $B_{1\text{-}5}$.

$\log 1/IC_{50} = 4.60 \log P - 0.471 \log P^2 + 0.90\ B_{1\text{-}5} - 5.66$

$n = 15,\ r = 0.96,\ s = 0.32,$ log Popt. 4.93, $F_{3,11} = 48.68$

B1 is the sterimol parameter for the width of the substituent in position 5 of the phenyl ring. For the same set of derivatives the following equation correlates the results from the in vivo carrageenin induced paw-edema (CPE) with log P and I_{-6}.

$\log 1/CPE = 0.94 \log P + 0.72\ I_{-6} + 1.01$

$n = 14,\ r = 0.873,\ s = 0.377,\ F_{2,11} = 24.95$

The indicator variable I_{-6} assigns a value of 1 for R_1 = phenyl group.

For the polyarthritis test (AAA) for 13 data points [17]:

$\log 1/(AAA) = 0.56 \log P + 0.81 B_{1\text{-}5} + 1.21$

$n = 11,\ r = 0.94,\ s = 0.24,\ F_{1,8} = 28.75$

For some thiazolyl and benzothiazolyl Schiff bases [18] which have been reported to act as possible soybean LOX inhibitors, a regression analysis was performed between their anti-inflammatory (CPE % percent induced inhibition of carrageenin mouse paw edema) and LOX inhibitory activities.

$\log CPE\ \% = 1.468\ LOX - 1.108$

$n = 7,\ r = 0.84,\ s = 0.059,\ F = 11.666$

Many NSAIDs are known to act either by inhibiting the production of free radicals or by scavenging them. The antioxidant (radical-trapping agents) can inhibit all types of fatty acid oxygenases (COX and/or LOX) and they might seem to be well suited to general anti-inflammatory use. An extensive study of the chemical structures of effective phenolic radical-trapping inhibitors indicated that the most effective inhibitors had two aromatic rings connected by a short bridge. Many phenolic antioxidant compounds inhibit LOX as well as COX activities, although some compounds are selective inhibitors. Flavonoids, e.g., can inhibit the 5-LOX that forms Leukotrienes. [19]. A number of ring substituted (E)- 4-phenyl-3-buten-2-ones [20] with anti-inflammatory activity were found to scavenge superoxide and hydroxyl radicals to an appreciable extent. Good correlation was obtained between superoxide scavenging and anti-inflammatory activity (CPE)

$CPE\ \% = 80.9 - 94.6\ IC_{50}\ O_2^-$

$n = 8,\ r = 0.86,\ s = 14.9,\ F = 17.8$

The correlation was not significant with the hydroxyl scavenging activity :

$CPE\ \% = 65.9 - 0.95\ IC_{50}OH$

$n = 8,\ r = 0.73,\ s = 20.37,\ F = 6.57$

For the same dataset the following correlation [21] was also derived :